REMARKS

Status of the Claims

Claims 1-6, 8-10, 12-21, 23-26, 36, 49-52 and 58-74 are in the application.

Claims 9 and 21 have been withdrawn from consideration.

Claims 1-6, 8, 10, 12-20, 23-26, 36, 49-52 and 58-74 have been rejected.

By way of this amendment, claims 16 and 20 and withdrawn claim 21 have been amended, claims 17-19, 23-26, 66, 67 and 73 have been canceled, and new claims 75-87 have been added.

Upon entry of this amendment, claims 1-6, 8-10, 12-16, 20, 21, 36, 49-52 and 58-65, 68-72, 73-86 will be in the application including pending claims 1-6, 8, 10, 12-16, 20, 36, 49-52 and 58-65, 68-72, 73-86, and withdrawn claims 9 and 21.

Summary of the Amendment

Claim 16 has been amended to be a dependent claim that is dependent on claim 10.

Claim 20 and withdrawn claim 21 have also been amended to be dependent on claim 10.

New claim 75 is dependent on claim 1 and refers to methods which further comprise administering a therapeutically effective amount of a tricarboxylate transporter inhibitor to the individual. Support for new claim 75 is found throughout the specification and claims as filed.

New claims 76-78 are dependent on claims 50, 14 and 61 respectively and refer to administration of an anti- anti-cancer antibody. Support for new claims 76-78 is found throughout the specification such as in paragraph [0046] of the specification as published November 8, 2007 as U.S. Patent Publication 20070259956.

New claims 79-81 refers to methods of treating an individual who has cancer that comprises cancer cells that have a high rate of aerobic glycolysis that comprise steps of identifying the cancer as a cancer that comprises cancer cells having a high rate of aerobic glycolysis that are transformed by activation of Akt or by deletion of PTEN and then administering to the individual a therapeutically effective amount of an ATP citrate lyase

inhibitor. Support for new claims 79-81 is found throughout the specification such as in paragraphs [0072], [0073], [0075] and [0077] of the specification as published November 8, 2007 as U.S. Patent Publication 20070259956.

New claim 82 is dependent on new claim 79 and corresponds to claims 8 and 20. The method of claim 79 comprising the step of administering to said individual a therapeutically effective amount of an ATP citrate lyase inhibitor; wherein said ATP citrate lyase inhibitor is (-) hydroxycitrate.

New claims 83 and 84 are dependent on new claim 79 and refer to types of cancer. Support for new claims 79-81 is found throughout the specification such as in Example 3 (paragraphs [0103] of the specification as published November 8, 2007 as U.S. Patent Publication 20070259956.

New claims 85-87 are dependent on new claim 79 and refer to combination therapies. Support for new claims 79-81 is found throughout the specification such as in paragraphs [0045] - [0047] of the specification as published November 8, 2007 as U.S. Patent Publication 20070259956.

New claims 75-87 each read on the elected species.

No new matter has been added.

Claim Rejection Under 35 U.S.C. § 103(a)

Kuhajda et al in view of Schroder et al

Claim 1-6, 8, 10, 12-15, 50-52, 58-65, 68-72 and 74 have been rejected under 35 USC 103(a) as unpatentable over Kuhajda et al. (US Patent No. 5, 759,837) in view of Schroder et al (1999 Int. J. Gynecol Cancer).

Kuhajda et al. discloses methods of treating individuals who have **cancer that is dependent on endogenously synthesized fatty acid.** According to Kuhajda et al. inhibition of fatty acid synthesis in such cancer cells can selectively eliminate such cells. Among the targets for inhibiting fatty acid synthesis disclosed by Kuhajda et al is citrate lyase. Kuhajda et al

teaches inhibiting citrate lyase in cancer cells dependent on endogenously synthesized fatty acid sufficient to inhibit fatty acid synthesis.

Schroder et al discloses use of PET to detect metastatic ovarian tumors.

It had been asserted that it would have been obvious to combine the teaching of Kuhajda et al and Schroder et al. to produce the present invention. Applicants respectfully disagree.

The present invention differs from the teaching in Kuhajda in fundamental and significant ways. Applicants have discovered that in cancer treatment, cells with a high rate of aerobic glycolysis display a high sensitivity to inhibition of ATP citrate lyase and that such inhibition can induce of apoptotic cell death. (see paragraph [0074]). In cells with a high rate of aerobic glycolysis, ATP citrate lyase is particularly useful as an apoptosis inducing agent because it inhibits the glycolysis pathway which leads to mitochondrial hyperpolarization and ultimately initiation of apoptotic cell death. Applicants' disclosure teaches that individuals who have cancer comprising cancer cells with a high rate of glycolysis can treated with an amount of citrate lysase inhibitors to induce apoptosis. The specification teaches that such cancer cells have an increased sensitivity to elimination using citrate lyase inhibitors. Nothing in Kuhajda teaches or suggests that in treating cancer, cancer cells which have a high rate of glycolysis are more sensitive to treatment with citrate lyase. As noted in the Official Action, while teaching that cancer cells dependent on endogenous fatty acid synthesis can be treated with citrate lyase inhibitors, Kuhajda does suggest that cancer which does not have elevated levels of fatty acid synthase can be treated with "fatty acid synthase inhibitors." Citrate lyase inhibitors are distinct from fatty acid synthase inhibitors. More importantly, Kuhajda does not recognize the link between cancer cell which exhibit elevated levels of glycolysis and the use of citrate lyase inhibition to induce apoptosis in cancer cells displaying such a metabolic profile. Such cancer cells are particularly susceptible to induction to undergo apoptosis by inhibition of citrate lyase.

One skilled in the art would not expect that inhibiting citrate lyase would particularly effective to induce apoptosis in cancer cells that exhibit a high rate of glycolysis. The use of citrate lyase inhibitors to treat cancers with cancer cells that have a high rate of glycolysis is not obvious because such cancer cells are unexpectedly more sensitive to citrate lyase inhibition as a

mechanism to induce apoptosis compared to cancer cells that do not have a high rate of glycolysis. Example 2 (paragraph [0073]) in the specification shows increased sensitivity of cancer cells to "undergoing apoptosis in response to ATP citrate lyase inhibition" and that "this sensitivity can be further enhanced by oncogenes that stimulate the aerobic glycolysis of such cells." The conclusion section of Example 2 states;

> Furthermore, sensitivity to ATP citrate lyase inhibition is much greater in proliferating cells than in nonproliferating cells and is dramatically enhanced in cells that have undergone oncogenic transformation that leads to the induction of aerobic glycolysis.

Applicants have discovered that cancer cells with high rates of aerobic glycolysis are more sensitive to citrate lyase inhibition. The invention refers to the selectively use of citrate lyase inhibitors against cancer cells which to have an elevated sensitivity to death by citrate lyase inhibitors, i.e. cancer cells with a high rate of glycolysis. PET may be used not simply as a tumor imaging technology but one that selectively images those tumors which have the elevated sensitivity to death by citrate lyase inhibitors.

Schroder combined with Kuhajda does not render the invention obvious. While Schroder teaches PET can be used to image some tumors, nothing in Schroder teaches or suggests that such tumors would have an elevated sensitivity to treatment with citrate lyase inhibitors. Other imaging techniques could be used to indentify cancer but PET identifies cancer which is susceptible to treatment with citrate lyase inhibitors. PET does not image all tumors, only those with elevated rates of glycolysis compared to adjacent tissue. Not all cancer is imaged using PET. Further, other technologies can be used to image cancer. However, the use of PET provides therapeutically useful information because tumors which can be imaged with PET can be treated with citrate lyase inhibitors. Imaging with MRI or CAT scan may detect tumors undetected with PET but PET informs the diagnostician of the suitability of using citrate lyase inhibitors. One skilled in the art viewing Kuhajda and Schroder would not conclude that it would be obvious to treat individuals with cancer detectable by PET with citrate lyase inhibitors

because the elevated sensitivity and susceptibility of such cancer to citrate lyase inhibitors is not obvious.

Nothing in the combination of Kuhajda and Schroder teach or suggest that high rates of glycolysis in cancer cells are an indicator of greater sensitivity to death by citrate lyase inhibition. The present invention is not obvious in view of the combination of Kuhajda and Schroder.

Claim 1-6, 8, 10, 12-15, 50-52, 58-65, 68-72 and 74 are not obvious in view of Kuhajda et al. (US Patent No. 5, 759,837) combined with Schroder et al (1999 Int. J. Gynecol Cancer). Applicants respectfully request that the rejection of claims 1-6, 8, 10, 12-15, 50-52, 58-65, 68-72 and 74 under 35 USC 103(a) as unpatentable over Kuhajda et al. (US Patent No. 5, 759,837) in view of Schroder et al (1999 Int. J. Gynecol Cancer) be withdrawn.

Kuhajda et al. in view of Schroder et al and further in view of Bru et al.

Claim 1-6, 8, 10, 12-20, 36, 49-52 and 58-74 stand rejected under 35 USC 103(a) as unpatentable over Kuhajda et al. (US Patent No. 5, 759,837) in view of Schroder et al (1999 Int. J. Gynecol Cancer) and further in view of Bru et al. (US Patent No. 5,219,846).

Kuhajda et al. and Schroder et al. are discussed above.

Bru et al. is cited as teaching the use of phosphoenolpyruvic acid to treat tumors.

It had been asserted that it would have been obvious to combine the teaching of Kuhajda et al and Schroder et al. and Bru et al. to produce the present invention. Applicants respectfully urge reconsideration of the rejection.

Initially, Applicants note that as examined claims 1-6, 8, 10, 12-15, 50-52, 58-65, 68-72 and 74 do not refer to directly or through dependency to tricarboxylate transporter inhibitor. As amended, claims referring to tricarboxylate transporter inhibitors.

Applicants respectfully urge that the combination of references neither teaches nor suggests that cancer cells with high rates of glycolysis have a higher sensitivity to citrate lyase inhibitors. As noted above, the combination of Kuhajda et al. and Schroder neither teaches nor suggests that cancer cells with high rates of glycolysis have an increased sensitivity to citrate

lyase inhibitors. Bru neither teaches nor suggests the unexpected increased sensitivity to citrate lyase inhibitors. The combination of Kuhajda, Schroder and Bru neither teaches nor suggests that cancer cells with high rates of glycolysis would be particularly susceptible to treatment with citrate lyase inhibitors. The present invention is not obvious to one skilled in the art.

Claim 1-6, 8, 10, 12-20, 36, 49-52 and 58-74 are not obvious in view of Kuhajda et al., Schroder et al. and Bru et al. Applicants respectfully request that the rejection of Claim 1-6, 8, 10, 12-20, 36, 49-52 and 58-74 under 35 USC 103(a) as unpatentable over Kuhajda et al. in view of Schroder et al. and further in view of Bru et al. be withdrawn.

Conclusion

Claims 1-6, 8, 10, 12-16, 20, 36, 49-52 and 58-65, 68-72, 73-86 are in condition for allowance. Applicants respectfully request that claims 9 and 21 be rejoined as additional species and that claims 1 -6, 8-10, 12-16, 20, 21, 36, 49-52 and 58-65,68-72, 73-86 be allowed at this time. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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